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TITLE: Determination of Optimum Vitamin D Nutrition in Young Women

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CONTRACTING ORGANIZATION: Creighton University
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14. ABSTRACT
The main objective of this proposal is to study the effect of increasing doses of vitamin D3 in a group of young women with hypovitaminosis D (serum 25OHD < 20 ng/ml) and an adequate calcium intake of 1200 -1400mg/day. This is a double blind randomized placebo controlled study .There will be 5 treatment arms, four vitamin D3 dose groups (400, 800, 1600, 2400 IU/day, placebo). Calcium citrate tablets will be given to maintain the calcium intake between 1200-1400mg/d. The study will recruit up to 120 Caucasian and 120 African American women subjects, ages 25 to 45. The primary outcomes are changes in serum 25OHD and serum PTH. Secondary outcomes are calcium absorption, physical performance tests and safety measurements of serum calcium and 24 hour urine calcium. The first year of active recruitment started on April 1 2008 and the first subject was randomized to treatment on 04/28/2008. For year one, we had 49 subjects randomized to treatment (20 African Americans, 29 Caucasians). After the first recruitment year we continued to recruit and build a list of potential subjects to contact the next recruitment period. In the second year of recruitment we used these contacts as well as several other methods. Active recruitment for the second year started in January 2009 and to date (October 2009) we have randomized to treatment 168 subjects (49 African Americans, 119 Caucasians).

15. SUBJECT TERMS
None provided.

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Annual Report
(Oct 2008-Sept 2009)

Grant/Cooperative Agreement Number:
Proposal No. PR065013, Award No.W81XWH-07-1-0201, HRPO Log No. A-14205

Grant/Cooperative Agreement Title:
Protocol, "Determination of Optimum Vitamin D Nutrition in Young Women"

Recipient:

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Grant Officer's Representatative:
Kathleen Taggert

Abstract

The main objective of this proposal is to study the effect of increasing doses of vitamin D_3 in a group of young women with hypovitaminosis D (serum 25OHD < 20 ng/ml) and an adequate calcium intake of 1200 -1400mg/day. This is a double blind randomized placebo controlled study .There will be 5 treatment arms, four vitamin D3 dose groups (400, 800, 1600, 2400 IU/day, placebo). Calcium citrate tablets will be given to maintain the calcium intake between 1200-1400mg/d. The study will recruit up to 120 Caucasian and 120 African American women subjects, ages 25 to 45. The primary outcomes are changes in serum 25OHD and serum PTH. Secondary outcomes are calcium absorption, physical performance tests and safety measurements of serum calcium and 24 hour urine calcium. The first year of active recruitment started on April 1 2008 and the first subject was randomized to treatment on 04/28/2008. For year one, we had 49 subjects randomized to treatment (20 African Americans, 29 Caucasians). After the first recruitment year we continued to recruit and build a list of potential subjects to contact the next recruitment period. In the second year of recruitment we used these contacts as well as several other methods. Active recruitment for the second year started in January 2009 and to date (October 2009) we have randomized to treatment 168 subjects (49 African Americans, 119 Caucasians).

Introduction

The diagnosis of vitamin D deficiency (serum 25OHD<12ng/ml) and vitamin D insufficiency (serum 25OHD<20ng/ml) have become more common in the last 3 years as health professionals became more aware of this issue. It has been suggested that a serum 25OHD level of 30ng/ml is optimal for bone health because serum parathyroid hormone levels are lower at this level and markers of bone resorption are decreased. It is also suggested that the RDA (Recommended Dietary Allowance) for vitamin D should use this serum 25OHD level as a goal when estimating the RDA. Because there have been no systematic dose response studies on vitamin D we postulate that the minimal dose of vitamin D that will achieve a serum 25OHD of 30 ng/ml in 97 percent of young women during the winter will exceed 1700 IU/day in Caucasian and 2000 IU/day in African American women. This is much higher than the present RDA of 400-600 IU/day which may need to be revised upwards if this hypothesis is confirmed.
To measure the dose response we will use vitamin D_3 doses of 400, 800, 1600, and 2400 IU/day plus a calcium intake of 1200-1400mg/day compared with a placebo group and similar calcium intake.

Body

Funding for this study started on October 6, 2007. The first six months involved development of a protocol, construction of subject charts, submission to the local IRB and approval by DOD. There was a significant delay in obtaining final approval by HRPO.

10/6/2006	Award Notice	Pamela Fisle
10/10/2006	Development of protocol and forms	
12/13/2006	Initiate document submission	Amber Stanley
1/25/2007	Protocol submitted to DOD	Dr. Gallagher
9/8/2007	IRB approval of protocol	Dr Gallagher
10/1/2007	Funding started	
10/16/2007	PEF comment	Johanna Kidwell
11/19/2007	Reply to PEF.	Dr. Gallagher
12/20/2007	PEF further comments.	Johanna Kidwell
1/10/2008	PEF further comments.	Johanna Kidwell
1/24/2008	Creighton IRB approval of protocol & forms.	Dr Gallagher
2/18/2008	UNMC IRB approval.	Dr Gallagher
2/19/2008	Study drug arrived.	
2/26/2008	DSMB Conference completed. No issues arose.	
3/19/2008	Final approval by HRPO.	
3/19/2008	Clinical trial registered NCT00662844.	
4/1/2008	Recruitment started.	
5/23/2008	Creighton IRB approval of consents revision (personnel change).	

9/16/2008	Creighton IRB renewal approval & consent revision (personnel change).
2/11/2009	Creighton IRB approval of protocol revision & consents (ethnic group size increase (100 to 120), Amendment 1.
3/13/2009	HRPO revision request to protocol & consents.
3/18/2009	Creighton IRB approval of protocol revision & consents.
3/27/2009	HRPO approval of protocol revision & consents.
9/15/2009	Creighton IRB renewal approval.

Recruitment: Because serum 25OHD is lowest in the months January to May we have a restricted window for recruitment. As a result of the delayed approval by HRPO we were only able to recruit for 2 months in the first year- 2008.

Summarizing our activity to date we have screened a total of 1316 women on the phone. 525 of the 648 qualified by phone screening and scheduling an informational screening visit came in and signed consent forms. Of the 504 that signed consent, 262 qualified on the basis of low serum 25OHD and 168 were randomized to a treatment group. A complete summary to date of our subject contact and recruitment is shown in table 1 in the appendix. This table illustrates some of the problems and difficulties associated with recruitment. Of those subjects that had a screening blood sample drawn, 52% qualify on the basis of low serum 25OHD; however, only 33% of those screened would eventually be randomized to study drug. Another issue is that 23% of those that schedule an informational screening meeting are 'no shows' and many of them are repeated 'no shows' even after rescheduling. The same can be seen of those subjects that qualify for randomization. 28% of these subjects do not get randomized to treatment ('no shows' or 'withdrew'). In the 'no show' category are those subjects who we have not been able to contact to date and have not returned phone messages. If any 'no show' has been contacted they may have come back or given us a reason why they are declining participation ('withdrew') and then have been moved out of the 'no show' category. We have employed visit reminder post cards and phone calls/messages as methods to help alleviate the 'no show' issue.

African American subjects have been difficult to recruit and we have taken steps this year to aid in recruitment. Recruitment flyer mailings, targeted mailings, multiple radio advertisements, recruiting booths at health events and recruitment informational events at companies have all been employed. Our goal has been to try and get a one-on-one informational session with a potential subject in order to make them feel comfortable with the project and staff.

Results: The mean serum 25OHD for 378 Caucasian women screened was 23.2 ± 10.1 ng/ml and for the 160 who qualified it was 14.5 ± 4.4 ng/ml. For the 126 African American women the mean for all those screened was 10.7 ± 5.7 ng/ml and for the qualifiers it was 10.5 ± 4.2 ng/ml. As defined, 42 percent of Caucasians and 81 percent of African Americans have vitamin D insufficiency as defined. On further examination of

the screening results it is shown that 12 percent of Caucasians and 66 percent of African Americans have vitamin D deficiency as defined.

Progress of Randomized Subjects: As of October 2009, 25 subjects have completed study (4 African Americans and 21 Caucasians) and 32 (19%) have dropped from study after randomization to treatment. Of those dropped, 'lost to follow up' (22) is the biggest category and contains those subjects that did not have a clearly defined reason for withdrawal. The majority (111) of randomized subjects are currently undergoing study visits.

Reportable Outcomes
There are no primary outcomes to report yet since most of the subjects are currently in the one year of treatment as per protocol. The outcomes to be studied are given below.

Primary outcomes of the study are serum 25OHD and PTH levels at the end of the first year of treatment.

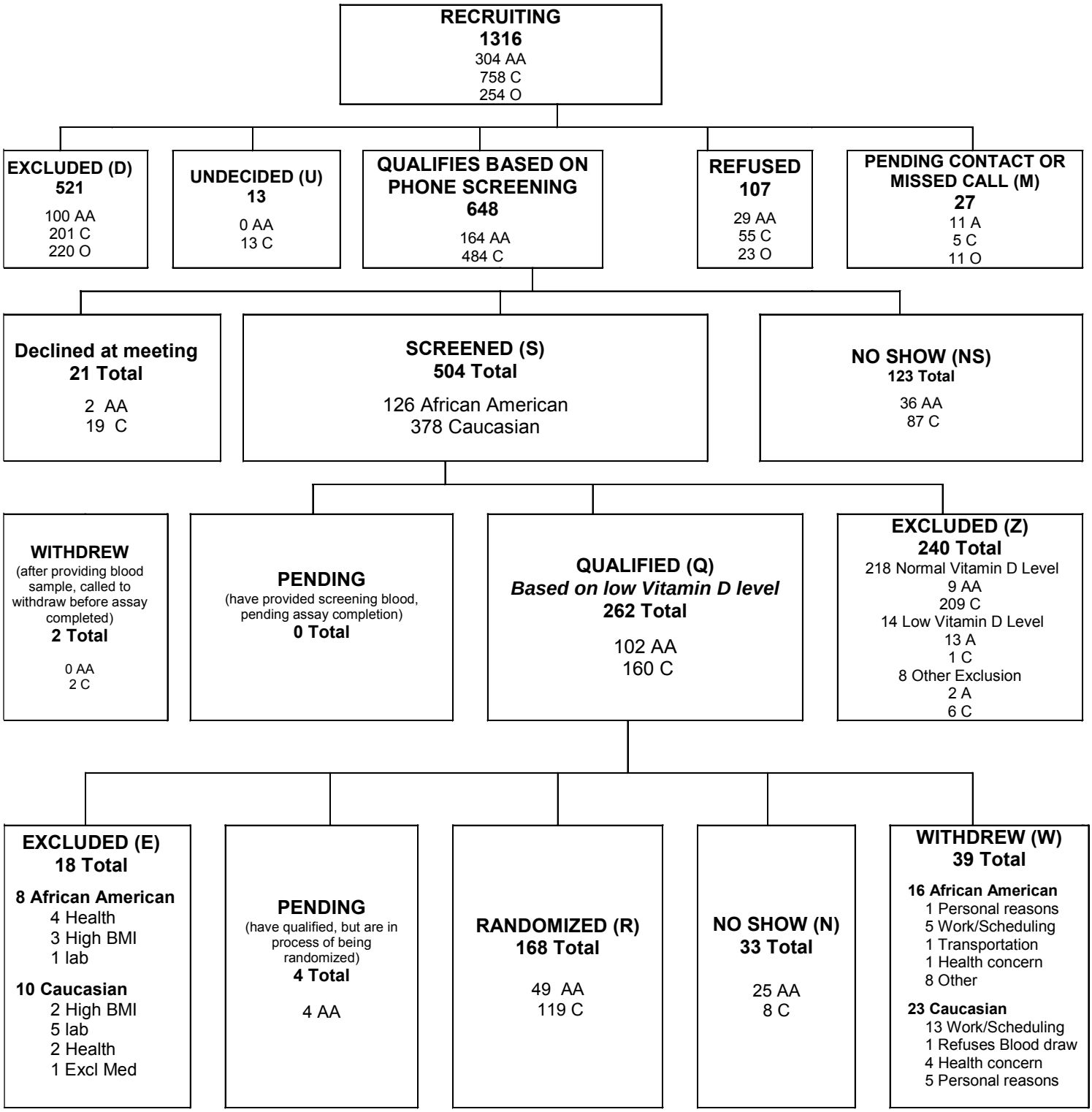
Secondary outcome measures are to study the safety of these doses on serum calcium and urine calcium.

Safety: Serum calcium and 24 hour urine calcium are measured every 3 months. Two subjects have developed hypercalciuria (> 400mg/24h). Both subjects followed the hypercalciuria management protocol and a re-test requested. On re-test, the 24 hour urine calcium of one subject dropped well below 400mg. The other subject refused multiple requests for re-test and was withdrawn from study. There have been no serious adverse events reported.

Conclusion
This study has insufficient data at this time to draw any conclusions, most of the subjects will finish protocol in the next 6 months and outcome data will be available in late 2010.

References
None.

Appendix - Table 1



Completed Study: 4 AA — 16 Drops AA 1 AE, 1 Pregnant, 1 Health Concern, 12 Lost, 1 Scheduling
21 C — 16 Drops C 2 Health Concern, 10 Lost, 1 Noncompliant, 1 Personal, 2 Scheduling

AA = African American
C = Caucasian
O = All other ethnic groups (excluded from study)